REMARKS

Claims 1-96 remain in the application. Claims 63, 81, and 89-94 are amended to insert a period (--.--) at the end of each claim.

Claims 1-96 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over Claims 1-4, 6-17, and 20-99 of U.S. Patent Application No. 2005/0020945.

The referenced patent application bears Serial No. 10/767,752, filed January 29, 2004, and is a continuation-in-part of the instant application and thus is later in time. Applicants' respectfully decline to submit a Terminal Disclaimer in the present application. However, if and when Applicants are presented with the obviousness-type double patenting rejection in the CIP application, they will consider filing such a Terminal Disclaimer in that application.

Claims 1-6, 11-16, 21-27, 30-36, 39-42, 49-56, 58, 60, 62-66, 69, 71-76, 78-79, 81-86, 88-90, and 92-96 are rejected under 35 USC 102(b) as being anticipated by Jolesz et al (U.S. Patent 5,752,515).

Jolesz et al, cited by Applicants in paragraph 0022 and discussed in their Information Disclosure Statement on page 10, filed on September 16, 2003, is directed to methods and apparatus for image-guided ultrasound delivery of compounds through the blood-brain barrier. Jolesz et al use ultrasound, therapeutically, ***only to open the blood brain barrier*** which is the outer thin covering layer over the actual brain matter underneath where Applicants' subject diseases (abnormal protein-related or prion-related diseases) reside. Jolesz et al use non-therapeutic ultrasound, i.e., diagnostic imaging ultrasound, to verify the favorable alteration of that cover layer-among other imaging modalities such as MRI. They do not teach ultrasonic therapeutic treatment of brain matter ***in*** the brain. Jolesz et al only teach drugs passing through their opened blood-brain-barrier or BBB and possibly passively chemically treating brain matter ***but not with at-depth ultrasonic*** help or preconditioning. Because they do not teach or suggest actual brain-matter ultrasonic or ultrasonic-supported therapy, they do not discuss any of the necessary aspects of the necessary acoustic beam and/or drugs to do so. Jolesz et al image at least a portion of the brain cover-layer in the vicinity of the selected BBB opening, e.g., via magnetic reso-

nance or ultrasound imaging. A compound, e.g., a neuropharmaceutical, in the patient's bloodstream is delivered to the confirmed opened BBB location by applying ultrasound to effect opening of the blood-brain barrier at that location in the brain cover-layer and ***not*** in the brain matter itself and, thereby, to induce uptake of the compound through the BBB covering such that it can diffuse into the underlying brain matter.

Applicants' Claim 1 recites:

> 1. A system for the *therapeutic treatment of abnormal protein-related or prion-related diseases of a human patient's brain or neurological system* comprising:
>
> (a) *acoustic exposure therapy means comprising at least one acoustic or vibration emitter for acoustically or mechanically coupling, directly or indirectly, acoustic or vibratory emissions into a brain or neurological region which has been, is, or is expected to potentially be subject to the nucleation, growth or deposition of abnormal-protein or prion-related deposits, nodules or bodies*;
>
> (b) means for exciting said emitter to emit acoustic or vibration energy with a desired characteristic; and
>
> (c) *said emitter adapted to deliver therapeutic acoustic or vibration energy, directly or indirectly, to at least one of said brain or neurological regions*, the therapy designed to provide, enable or accelerate at least one of the following therapy processes:
>
> (i) physical breakup, breakdown, erosion, dispersion, disentanglement, de-aggregation, redistribution, dissolution, de-agglomeration, de-amalgamation or permeation of at least some said deposits, nodules or bodies,
>
> (ii) interference in, slowing of, or reversal of at least one physical, chemical, biological or genetic deposit, nodule or body formation-process, formation-sequence or formation pathway anywhere in the process, sequence or pathway, and
>
> (iii) aiding the recovery, growth, regrowth, new growth or improved chemical, physical, biological, genetic or cognitive functionality of brain-related or neurological-related cells, physiology or functional pathways negatively impacted or stressed by the deposition of, formation of, or presence of said deposits, nodules or bodies or their associated formation processes.

(Emphasis added.)

Applicants' independent Claim 86 recites:

> 86. A method for the *therapeutic treatment of abnormal protein-related or prion-related diseases of a human patient's brain or neurological system* comprising:
>
> (a) acoustically coupling said patient's brain or neurological system to *acoustic therapy means comprising at least one acoustic or vi-*

bration emitter for acoustically or mechanically coupling, directly or indirectly, acoustic or vibratory emissions into a brain or neurological region which has been, is, or is expected to potentially be subject to the nucleation, growth or deposition of abnormal-protein or prion-related deposits, nodules or bodies;

(b) exciting said emitter to emit acoustic or vibration energy with a desired characteristic; and

(c) *delivering therapeutic acoustic or vibration energy from said emitter, directly or indirectly, to at least one said brain or neurological region, the therapy designed to provide, enable, accelerate or initiate at least one of the following therapy processes*:

(i) physical breakup, breakdown, erosion, dispersion, disentanglement, de-aggregation, redistribution, dissolution, de-agglomeration, de-amalgamation or permeation of at least some said deposits, nodules or bodies,

(ii) interference in, slowing of, or reversal of at least one physical, chemical, biological or genetic deposit, nodule or body formation-process, formation-sequence or formation pathway anywhere in the process, sequence or pathway, and

(iii) aiding the recovery, growth, regrowth, new growth or improved chemical, physical, biological, genetic or cognitive functionality of brain-related or neurological-related cells, physiology or functional pathways negatively impacted or stressed by the deposition of, formation of, or presence of said deposits, nodules or bodies or their associated formation processes.

(Emphasis added.)

Applicants' independent Claim 88 recites:

88. A system for the *therapeutic treatment of abnormal protein-related or prion-related diseases of a human patient's brain or neurological system* comprising:

(a) means to direct acoustic or vibrational energy *into or through at least one such diseased or potentially diseased anatomy portion*; and

(b) an optional drug, medicament or controlled dietary content capable of contributing to the therapy also directly or indirectly delivered to the portion,

wherein the acoustics and optional drug together at least slow a cognitive loss process by slowing , stopping or reversing a deposition process.

(Emphasis added.)

Applicants' independent Claim 95 recites:

95. A method of at least temporarily slowing, stopping or avoiding a patient's cognitive losses *associated with a neural deposition disease* comprising administration of acoustic or vibrational energy into affected or po-

> tentially affected patient anatomy portions, *said energy altering, blocking or reversing a cognitively-damaging deposition process*, at least temporarily.

(Emphasis added.)

Applicants' independent Claim 96 recites:

> 96. A system for at least temporarily slowing, stopping or avoiding a patient's cognitive losses *associated with a neural deposition disease* comprising administration of acoustic or vibrational energy controllably emitted from an acoustic emitter into affected or potentially affected patient anatomy portions, *said energy altering, blocking or reversing a cognitively-damaging deposition process*, at least temporarily.

(Emphasis added.)

The Examiner argues that Jolesz et al disclose a method and apparatus for treating neurological disorders by ultrasonic delivery of compounds through the blood barrier, citing Col. 3, lines 44-67.

While this is accurate as far as it goes, by "through the blood barrier" is actually meant to "open the blood barrier and thereby induce delivery *sic: of]* a compound from the patient's bloodstream to the location at that point" (Col. 5, lines 2-6). Throughout the patent, Jolesz et al continually state that their phase array 12 operates to deliver ultrasound, through the patient's skull, in doses suitable for inducing non-destructive imaging-detectable change (e.g., heating, cavitation or uptake of contrast agent) and/or non-destructive ***opening*** of the blood-brain barrier at selected locations within the brain; see, e.g., Col. 5, lines 26-31.

Jolesz et al are simply using ultrasound to deliver compounds through the blood-brain barrier and applying ultrasound to effect in the BBB ***layer*** and/or fluids at that location a change detectable by imaging.

Quite differently, Applicants are using ultrasound to treat ***foreign*** material at-depth, e.g., plaque, in the brain. Alternatively, Applicants treat at-depth brain matter thought to be susceptible to future foreign material deposition. In any event, Applicants are performing an at-depth brain-matter based ultrasonic or ultrasonically assisted therapy. Jolesz et al are performing an at-depth chemical treatment which is ***not*** ultrasonically enhanced. This is a fundamental difference. The subject tissues in the brain matter in one case are seeing a drug alone (Jolesz et al) and in Applicants' case, the subject tissues in the brain

matter are seeing an acoustically enabled or accelerated action of a drug ***or*** the beneficial effect of the acoustics alone.

Further, once the drug in Jolesz et al passes across the BBB, it can diffuse anywhere; there is no focus of therapeutic action at-depth. In Applicants' claimed invention, whether using ultrasound or ultrasound plus drugs, the therapeutic action is concentrated in the acoustic beam. Thus, Applicants' invention is more spatially selective, which is not surprising, since Applicants have a highly defined beam contributing to the at-depth therapy. Further, because Applicants utilize at-depth therapeutic ultrasound, Applicants have access to a wider range or degree of therapeutic benefits, with or without a drug, than do Jolesz et al. The aspect of at-depth therapeutic ultrasound is disclosed, for example, in paragraphs 0177 and 0178, with reference to FIG. 2.

To be technically precise, Jolesz et al do not even treat brain matter using acoustics, particularly not any brain matter subject to deposition diseases.

The independent claims (e.g., claims 1 and 86) are specifically limited to "therapeutic treatment of abnormal protein-related or prion-related diseases of a human patient's brain or neurological system", which includes

> "said emitter adapted to deliver therapeutic acoustic or vibration energy, directly or indirectly, to at least one of said brain or neurological regions, the therapy designed to provide, enable or accelerate at least one of the following therapy processes:
>
> (i) physical breakup, breakdown, erosion, dispersion, disentanglement, de-aggregation, redistribution, dissolution, de-agglomeration, de-amalgamation or permeation of at least some said deposits, nodules or bodies,
>
> (ii) interference in, slowing of, or reversal of at least one physical, chemical, biological or genetic deposit, nodule or body formation-process, formation-sequence or formation pathway anywhere in the process, sequence or pathway, and
>
> (iii) aiding the recovery, growth, regrowth, new growth or improved chemical, physical, biological, genetic or cognitive functionality of brain-related or neurological-related cells, physiology or functional pathways

negatively impacted or stressed by the deposition of, formation of, or presence of said deposits, nodules or bodies or their associated formation processes."

Jolesz et al simply fail to teach these limitations, which limitations are directed to ultrasonic treatment of deposits, nodules or bodies, otherwise known as foreign matter. An apparatus including an emitter that is adapted to deliver therapeutic acoustic or vibration energy within the brain for treating abnormal protein-related or prion-related diseases is hardly disclosed or suggested by apparatus for ultrasonic delivery of compounds through the blood-brain barrier.

"A claim is anticipated [under 35 U.S.C. § 102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987. See M.P.E.P. § 2131. For at least these reasons, the rejection of claim 1 and its dependent claims (Claims 2-6, 11-16, 21-27, 30-36, 39-42, 49-56, 58, 60, 62-66, 69, 71-76, 78-79, and 81-85) based on Jolesz et al should be reconsidered and withdrawn.

Independent Claim 86 contains essentially the same limitations as Claim 1 discussed above, and thus this claim is also patentable over Jolesz et al for at least the same reasons that Claim 1 is patentable. Further, Claim 87, which depends from Claim 86, is patentable over Jolesz et al for at least the same reasons that claim 86 is patentable.

Independent Claim 88 is directed to a system for the therapeutic treatment of abnormal protein-related or prion-related diseases of a human patient's brain or neurological system comprising, inter alia, means to direct acoustic or vibrational energy into or through at least one such diseased or potentially diseased anatomy portion; and an optional drug, medicament or controlled dietary content capable of contributing to the therapy also directly or indirectly delivered to the portion, wherein the acoustics and optional drug together at least slow a cognitive loss process by slowing, stopping or reversing a deposition process.

Jolesz et al are totally silent on a system for the therapeutic treatment of such diseases as well as means for directing acoustic or vibrational energy into or through a dis-

eased or potentially diseased portion to slow, stop, or reverse a deposition process. Thus, claim 88 and claims 89-90 and 92-94 dependent thereon are patentable over Jolesz et al.

Independent claims 95 and 96 recite slowing, stopping or avoiding cognitive losses associated with a neural deposition disease, which includes administration of an acoustic or vibrational energy to alter, block, or reverse deposition processes.

Jolesz et al utterly fail to disclose or suggest such treatment of neural deposition diseases, and it is not obvious that their imaging and/or delivering methods would provide such treatment. Thus, claims 95 and 96 are also patentable over Jolesz et al.

It is by no means clear that the ultrasound exposure of tissues taught by Jolesz et al will in any way serve to treat abnormal protein-related or prion-related diseases of the brain or neurological system.

The Examiner cites Col. 3, lines 44-67 of Jolesz et al as teaching treatment of neurological disorders. The actual disorders are listed in lines 63-67: "tumors, cancer, degenerative disorders, sensory and motor abnormalities, seizure, infection, immunologic disorder, mental disorder, mental disorder, behavioral disorder, and localized CNS disease". However, not one of the listed diseases can be said to comprise "abnormal protein-related or prion-related diseases of the brain or neurological system" as claimed by Applicants. Treatment of the diseases listed by Jolesz et al in no way discloses or even remotely suggests treatment of the types of diseases recited in Applicants' claims. Specifically, the diseases listed in Applicants' claim 1 are plaque-related. These are foreign materials, not living tissue and not diseased tissue.

While the Examiner has indicated that one specific claimed disease that is allowable is Alzheimer's Disease, recited in claim 28, the Examiner has provided no reason why Claim 27, which lists a broader number of abnormal protein-related or prion-related diseases, is rejected. Jolesz et al utterly fail to disclose treatment of such diseases. All such diseases are related to the formation of plaque, and are not taught by Jolesz et al and thus all are patentable over Jolesz et al.

Reconsideration of the rejection of Claims 1-6, 11-16, 21-27, 30-36, 39-42, 49-56, 58, 60, 62-66, 69, 71-76, 78-79, 81-86, 88-90, and 92-96, as amended, under 35 USC 102(b) as being anticipated by Jolesz et al is respectfully requested.

Claims 1, 7-10, 17-20, 41, 43, 59, 61, 77, 88, and 91 are rejected under 35 USC 102(e) as being anticipated by Brisken et al (U.S. Patent 6,464,6800.

Brisken et al disclose ultrasound enhancement of drug injection. A method of enhancing cellular absorption of a substance delivered into a target region of a patient's body, comprises: (a) delivering the substance to the target region, and (b) directing vibrational energy to the target region, wherein the vibrational energy is of a type and in an amount sufficient to enhance absorption into cells of the target region.

Applicants' independent Claims 1 and 88 are discussed above.

Like Jolesz et al, Brisken et al utterly fail to disclose or suggest the treatment of "abnormal protein-related or prion-related diseases". The Examiner cites Col. 12, lines 4-14 of Brisken et al as teaching the treatment of abnormalities of the brain. However, in the particular portion cited, the only abnormality taught is "soft tissue lesions 400" (line 7), such as cancerous lesions of the brain (lines 13-14). However, such disclosure does not even remotely suggest the treatment of "abnormal protein-related or prion-related diseases" as claimed. Specifically, the types of diseases listed in Applicants' claim 1 are plaque-related. These are foreign materials, not living tissue and not diseased tissue.

"A claim is anticipated [under 35 U.S.C. § 102] only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987. See M.P.E.P. § 2131. For at least these reasons, the rejection of claims 1 and 88 and their dependent claims based on Brisken et al should be reconsidered and withdrawn.

Reconsideration of the rejection of Claims 1, 7-10, 17-20, 41, 43, 59, 61, 77, 88, and 91, as amended, under 35 USC 102(e) as being anticipated by Brisken et al is respectfully requested.

Claims 37, 38, 57, and 92 are rejected under 35 USC 103(a) as being unpatentable over Jolesz et al, *supra*, in view of Hynynen et al (U.S. Patent 6,514,221).

The Jolesz et al reference is discussed above. Hynynen et al, cited by Applicants in paragraph 0022 and discussed in their Information Disclosure Statement on page 10, filed on September 16, 2003, is directed to the blood-brain barrier opening. A method of opening a blood-organ barrier of a subject includes providing an exogenous agent config-

ured to facilitate opening of the blood-organ barrier, administering the exogenous agent to desired region of the subject, and applying energy to the desired region of the subject while the exogenous agent is present in the desired region, the energy being in a blood-organ-barrier-opening amount sufficient to induce opening of the blood-organ barrier of the subject with the exogenous agent present and below a damage amount sufficient to induce thermal damage to tissue in the absence of the exogenous agent.

Claims 37, 38, and 57 depend from claim 1, which has been shown above to be patentable over Jolesz et al. Claim 92 depends from claim 88, which has been shown above to be patentable over Jolesz et al.

The teachings of Hynynen et al add nothing, since this reference, like Jolesz et al utterly fails to disclose or even remotely suggest the treatment of "abnormal protein-related or prion-related diseases", as claimed. Opening the blood-brain barrier and treating the brain with ultrasound, by itself, is simply insufficient to disclose treatment of foreign material in the brain.

"To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). M.P.E.P. § 2143. Accord, M.P.E.P. § 706.02(j). For at least these reasons, the rejection of claims 37, 38, 57, and 92 based on Jolesz et al and Hynynen et al should be reconsidered and withdrawn.

Reconsideration of the rejection of Claims 37, 38, 57, and 92, as amended, under 35 USC 103(a) as being unpatentable over Jolesz et al in view of Hynynen et al is respectfully requested.

The Examiner indicates that Claims 28-29, 44-49, 54-55, 67-68, 70, 80-81, and 87 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants appreciate that these claims are allowable. However, for the reasons given above, the remaining claims in the application are also considered to be patentable.

The foregoing amendments and arguments are submitted to place the application in condition for allowance. The Examiner is respectfully requested to take such action. If

the Examiner has any questions, he is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,

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